REMARKS

Claims 1-49 were pending. Claims 7-8 and 34-49 have been withdrawn as a result of an earlier Restriction Requirement. Applicants retain the rights to pursue claims 7-8 and 34-49 in a divisional application. Claims 3 and 4 have been cancelled. Claims 1, 2, 5, 6, 10, 12-15, 17, and 31 have been amended. Claims 50-52 are new. Upon entry of the present amendments, Claims 1-2, and 5-52 will be pending in this application. Claims 7-8 and 34-49 remain withdrawn from consideration. Claims 1-2, 5, 8, 9-33, and 50-52 are under active examination in this application.

Claim 1 has been amended to recite that the polymer matrix binds specifically and selectively to the prion protein. Support for this amendment can be found in the specification, *inter alia,* on page 5, second paragraph.

Claim 2 has been amended to recite that detecting the complex can be achieved prior to a separation process from the sample, after a separation process from the sample, or both. Support for this claim can be found in cancelled claims 3 and 4.

Claim 5 has been amended to recite that the polymer matrix is attached to a functional group comprising a positively charged group, a negatively charged group, an uncharged group, or a combination thereof. Support for this claim can be found in original Claim 1.

Claim 6 has been amended to correct an antecedent basis therein.

Claim 10 has been amended to recite that the amine group of the functional group is a primary amine group, a secondary amine group, a tertiary amine group, a quaternary amine group, or a combination thereof. Support for this amendment can be found in the original claim 10 and in specification, *inter alia,* on page 12, last paragraph.

Claim 12 has been amended to correct an antecedent basis therein.

Claims 13-15 have been amended to more clearly recite the subject matter claimed. This amendment is formal in nature and replaces the transitional phrase "is" with "comprising". Support for this amendment can be found throughout the specification.

Claim 17 has been amended to more clearly recite the subject matter claimed. This amendment is formal in nature. Support for this amendment can be found in original claim 17 and in the specification, *inter alia*, on page 10, first paragraph.

Claim 31 has been amended to correct an antecedent basis therein.

Claims 50-52 are new. Claim 50 recites that the functional group comprises a hydrophilic group, a hydrophobic group, an amphiphilic group, or a combination thereof. Support for this claim can be found in original claim 1, and the specification at page 10, last paragraph.

New claim 51 recites that the binding material comprises two or more binding materials having the same or different functional groups and the samples are contacted with the two or more binding materials simultaneously or in succession. Support for this claim can be found in the specification, *inter alia*, on page 12, second paragraph.

New claim 52 further defines the separation processes of amended claim 2 to include chromatography, solid support, membrane separation, reactor separation, magnetic separation, immunoseparation, colloidal separation, or a combination thereof. Support for this claim can be found in the specification, *inter alia*, in paragraph bridging pages 9-10.

I. Claim Rejections Under 35 U. S. C. § 112, Second Paragraph

The Examiner rejects Claims 14 and 15 as containing trademarks/trade names such as FRACTOGEL™ EMD, TOYOPEARL™, TSK-GEL™, and TOYOPEARL™ AMINO

650. Specifically, the Examiner contends that where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. § 112, second paragraph because the trademark or trade name cannot be used properly to identify any particular material or product. The Examiner asserts that in the present case the trademark/trade name is used to identify/describe the polymer matrix and, accordingly, the identification/description is indefinite. While the Examiner notes that a trademark or trade name can be used to identify a source of goods, it is the Examiner's position that in the present case the trademark name is used to identify the goods as polymer matrix and not the source of the goods. Applicants respectfully traverse the Examiner's rejection for the following reasons.

Applicants respectfully submit that the presence of the trademark names in claims 14 and 15 are proper. As the Examiner notes, the use of a trademark or trade name in a claim is not, *per se*, improper under 35 U. S. C. §112, second paragraph, but the claim should be carefully analyzed to determine how the mark or name is used in the claim. *See*, Manual of Patent Examination Practice (MPEP) section 2173.05(u). As the Examiner has correctly pointed out, it is important to recognize that a trademark or trade name is used to identify a source of goods, and not the goods themselves. It is suggested that names used in trade are permissible in patent applications if: (A) Their meanings are established by an accompanying definition which is sufficiently precise and definite to be made a part of a claim, or (B) their meanings are well-known in this country. *See*, MPEP § 608.01(v).

Applicants respectfully submit that in the instant case the FRACTOGEL, TOYOPEARL and TSK-GEL are used to identify/describe the source of the polymer matrix used as the binding

agent. Additionally, the structures of the recited of polymer matrixes are sufficiently established and precise, as well as the fact that the main structures of these polymers matrixes are well known in this country. [1] Accordingly, Applicants believe that the Examiner's rejections of claims 14 and 15 under 35 U. S. C. §112, second paragraph for the use of the aforementioned trademarks were improper. Reconsideration and withdrawal of this rejection is respectfully requested.

II. Claim Rejections Under 35 U. S.C. § 102 (b)

The Examiner rejects Claims 1-6, and 9-33 under 35 U. S.C. § 102(b) as allegedly being anticipated by Foster *et al.*, as evidenced by Data Sheet and manual (Affinity Chromatography, Tosoh Bioscience LLC, Cat # 28 A21DS).

In particular, the Examiner contends that Foster *et al.* disclose a method of removal of prion protein from human plasma using Toyopearl amino 650M. The Examiner asserts that DEAE-Toyopearl™ 650M is the same as Toyopearl™ amino 650 and Toyopearl™ AF amino 650 M and therefore, Toyopearl™ used by Foster *et al.* is the same Toyopearl™ recited in the instant claims. The Examiner further asserts that the limitation of forming and detecting a complex between a prion protein in a sample and prion protein binding material are encompassed

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[1] The Examiner has indirectly supported the fact that the recited trademarks indeed identify the source of polymer matrices by asserting that Toyopearl ™, DEAE-Toyopearl™ 650M, Toyopearl™ amino 650 and Toyopearl™ AF amino 650 M are the same since they are all derived from Toyopearl ™ as the source polymer matrix. *See*, the Examiner's rejections of claims under 35 U.S.C. §§ 102 and 103.

by the method of removal of prion protein disclosed by Foster *et al.* and therefore, Foster *et al.* anticipate the subject matter of the instant claims. Applicants respectfully traverse the Examiner's rejections for the following reasons.

Applicants respectfully submit that Foster *et al.*, do not disclose the method of the invention as claimed. Claim 1 as amended recites a method of forming a complex between a prion protein and a prion protein binding material in a sample comprising contacting the sample with the prion protein binding material under conditions allowing formation of the complex between the prion protein and the prion protein binding material, wherein the prion protein binding material comprises a polymer matrix that binds *specifically and selectively* to the prion protein.

The claims of the instant invention require that the polymer matrix binds specifically and selectively to the prion protein. Foster *et al.*, do not teach this requirement. Foster *et al.* at best disclose a tangentional, non-selective and non-specific absorption of the chromatographic matrix to prion protein during the process of isolation of fibrinogen from blood. According to Foster *et al.* any adventitious absorption of the prion protein to the chromatography matrix is because of the adherent nature of prion protein. *See*, Foster *et al.* page 92. The non-specific and general absorption of prion protein is also evident from Foster *et al.*'s conclusion that a high degree of prion protein is removed by filtration.

> "[T]he observation that a high degree of PrP^{SC} removal can be obtained by depth filtration (table 1) may be the most important finding from our study, as depth filtration are standard items used in most albumin and immunoglobulin processes. In addition, the low cost of filter media means that filter pads are normally disposed of after each use, thereby avoiding the

> possibility that subsequent product batches could be exposed to any TSE infectivity which might have been adsorbed."

Foster *et al.*, Page 94, second Column, second paragraph.

Foster *et al.* do not clearly specify whether PrP was bound to the column or was it in the flow through. This reference postulates that "given its adherent nature" prion protein may have remained absorbed to chromatographic matrices following product elution. This finding is contrary to the method of the invention that requires polymer matrices that binds specifically and selectively to the prion protein.

Accordingly, Foster *et al.* is not an anticipatory reference because it does not disclose any specific and selective binding of prion protein to the polymer matrix, as required by claims 1-2, 5, 8, 9-33, and 50-52 of the invention as claimed.

Tosoh Bioscience LLC discloses the use of Tyopearl AF amino 650-M in chromatography. This publication does not disclose the method of forming a complex between a prion protein and a prion protein binding material in a sample as claimed. The Tosoh Bioscience publication is silent with respect to any specific target molecule that can be isolated or separated by the process of chromatography using specific Toyopearl resins disclosed, less so an indication that prion proteins can indeed be the target molecules and specific and selective binding of the prion protein to this resin.

Accordingly, Applicants respectfully submit that Foster *et al.* either alone or in combination with Tosoh Biosciences LLC, does not anticipate the invention as claimed.

Reconsideration and withdrawal of this rejection is respectfully requested.

III. Claim Rejections Under 35 U. S.C. § 102 (e)

Claims 1-6, and 9-33 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Hammond *et al.* (U.S. Patent No. 6,750,025). Specifically, the Examiner contends that Hammond *et al.* identify a ligand for prions and the identified ligand may be used either for the detection of prions, or for the removal of prions from a sample. The Examiner further asserts that as means for carrying out the invention, Hammond *et al.* teach that the ligand may be attached to the affinity column formed on a resin, including on Toyopearl resins which is identified as a Toyopearl amino 650 M resin. Based on this disclosure, the Examiner believes that Hammond *et al.* anticipate the invention as claimed. Applicants respectfully traverse the Examiner's rejections for the following reasons.

Hammond *et al.* is directed to a detection and separation method in which in general neither the target nor the ligand is known, with the exception of Example 5 in which the target is specified as prion protein. The detection method disclosed in Example 5, however, is different from the detection method of the invention. The gist of Hammond *et al.* is in the detection and characterization of an unknown ligand and an unknown target molecule that binds to that ligand. Hammond *et al.* 's method to detect an unknown target that binds to an unknown ligand is based on a positioning experimentation that requires physical positioning of an unknown target or ligand-target complexes within a first matrix such as agarose and elution of the target onto a second matrix such as nitrocellulose or PVDF (polyvinylidene fluoride) that are used to capture non-specifically most, if not all proteins eluted from the ligand-target complexes. This is

followed by a comparison between different positions of the ligand-support complexes and the target-ligand-support complexes in order to characterize a target.

Specifically, Hammond *et al.* 's characterization of a target and a ligand additionally requires transferring at least a portion of the target from the target-ligand-support complex to a second matrix so that the ligand-support complex of the target-ligand-support complex remains in the first matrix. In this way, Hammond *et al.* state that the position of the target within the second matrix corresponds to the position of the ligand-support complex within the first matrix which bound the target protein, the target on the second matrix is detected and ultimately the target that binds to a ligand is identified and may later be characterized. The identity of the target, the ligand and the ligand support complex is unknown in Hammond *et al.*, and therefore Hammond *et al.* cannot teach the use of specific set of ligands that will specifically bind to prion protein targets.

In contrast, the present invention as claimed is directed to a detection and separation method in which both the target and a general class of ligands are known. The invention provides methodology for detection and separation of prion protein using several ligands and provides comparative results of the specificity of each ligand to bind prion proteins from blood and brain samples. The invention does not require the immobilization steps of Hammond *et al.* for positioning the target or ligand-target complexes on a matrix (*i.e.*, gel) in order to detect or characterize a target or a ligand.

Applicants wish to emphasis that the term "matrix" is used differently between the instant application and Hammond *et al.* Matrix in the instant application refers to the polymeric backbone of the ligand and therefore it is covalently attached to the ligand. On the other hand,

matrix in Hammond *et al.* is not covalently attached to the ligand and refers to a compartment that functions in the immobilization of the ligand support or the ligand support target complexes. The first matrix in Hammond *et al* is an agarose gel such as those commonly used for electrophoresis and the second matrix is the nitrocellulose membrane, neither of which has any correlation with the structure of the ligand itself.

Accordingly, Applicants respectfully submit that Hammond *et al.* do not anticipate the invention as claimed. Reconsideration and withdrawal of this rejection is respectfully requested.

IV. Claim Rejections Under 35 U. S. C. § 103

The Examiner rejects Claims 1-6, and 9-33 under 35 U.S.C. §103(a) as allegedly being obvious over Prusiner (U.S. Patent No. 6,221,614 B1) in view of Kragten *et al.* (1998, *J Biol Chem* 273: 5821-28) as evidenced by Data Sheet and manual (Affinity Chromatography, Tosoh Bioscience LLC, Cat # 28 A21DS).

Specifically, the Examiner contends that Prusiner teaches a method for detection and removal of prions from blood plasma comprising forming a complex between the prion molecule and a complexing agent. The Examiner refers to claim 1 and claim 6 of the present invention to support this position. The Examiner further asserts that an example of the complexing agent taught by Prusiner is a polymer matrix coupled to a hydrophobic ligand and refers to column 12, lines 30-55 of this patent to support this position. While the Examiner notes that Prusiner does not specifically teach the use of a polymer matrix, such as Toyopearl amino 650, it is the Examiner's position that this deficiency is cured by the disclosure of Kragten *et al.*

The Examiner contends that Kragten *et al.*, teach a method for affinity precipitation of protein using polymer matrix Toyopearl AF amino 650 M resin as indicated on Page 5822, 3rd paragraph under Experimental Procedures. The Examiner believes that the teachings of Kragten *et al.* demonstrate that the polymer matrix is a known substrate for use in affinity-based separation of proteins from samples. Accordingly, it is the Examiner's position that one of the ordinary skill in the art at the time the invention was made would have been motivated to use Toyopearl AF amino 650 M resin to form complexes with prion molecules and subsequently detect the formed complexes, because Prusiner suggests the use of polymer matrixes for detection of prion molecules and because Toyopearl AF amino 650 M is a commonly used substrate for protein purification as taught by Kragten *et al.* and as evidenced by Data Sheet for Toyopearl AF amino 650 M product. Applicants respectfully traverse Examiner's rejection for the following reasons.

Applicants respectfully submit that where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed Cir. 1988). As the Federal Circuit emphasized "[B]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure." Id.

Neither of the references cited by the Examiner, either alone or in combination, teach or suggest the subject matter of claims 1-2, 5, 8, 9-33, and 50-52 as amended.

Applicants respectfully submit that neither Prusiner nor Kragten *et al*, either alone or in combination render the subject matter of the invention as claimed obvious. The present invention as claimed requires specific and selective binding of the polymer matrix to prion protein. Prusiner does not teach or suggest the subject matter of the claimed invention because Prusiner does not disclose the specific and selective binding of prion protein to a polymer matrix as required by the invention as claimed, less so specific and selective binding of the prion protein to a Toyopearl resin.

Prusiner discloses flow through columns and substrates such as spherical polymer beads, to remove prions from liquid samples. The prion protein of Prusiner does not directly bind to the polymeric material; rather it binds to a prion complexing agent. Prusiner's substrate (*e.g.*, polymeric materials) is coated with a prion complexing agent, such as a metal salt of a heteropoly acid (*e.g.*, phosphotungstic acid and its salts thereof.) By passing the blood sample through the column, the prion protein contained in the sample binds directly to the metal salt that is coated on the surface of the polymer beads. Further, Prusiner discloses a laundry list of materials that may bind to prion protein complexing agents (*i.e.*, the metal salts). None of these materials is the polymeric binding materials of the invention as claimed.

Kragten *et al.* do not cure the deficiency of Prusiner with respect to the method of detection of prion protein as claimed because Kragten *et al.* do not disclose binding of prion protein to a polymeric matrix. The affinity binding method of Kragten *et al.* is a solid phase chromatography that uses Toyopearl AF amino 650 M resin to immobilize a neuroprotective and

anti-apoptosis protein (*i.e.*, CGP 3466). This protein is completely unrelated to blood proteins and specifically is unrelated to prions.

Kragten *et al.*, demonstrate binding of CGP 3466 to glyceraldehyde-3-phosphate dehydrogenase by affinity binding or affinity labeling. CGP 3466 is an analogue of R-o-Deprenyl (Selegiline) that is currently used for the treatment of Parkinson's disease. There are a myriad of proteins that can be used in a solid phase chromatography. One of ordinary skill in the art following the teachings of Kragten *et al.*, demonstrating the use Toyopearl AF amino 650 M resin to immobilize CGP 3466 prior to binding of CGP 3466 to glyceraldehyde-3-phosphate dehydrogenase by affinity binding would have no reason or motivation to attempt to remove a completely unrelated protein from a blood sample by using a Toyopearl resin.

Applicants respectfully submit that the teaching of Kragten *et al.*is insufficient to remedy the deficiencies of the primary reference and to render obvious any claims of this application.

Additionally, Applicants submit that the combination of the Prusiner and Kragten *et al.* cannot be properly made. Obviousness cannot be established by combining pieces of prior art absent some teaching, suggestion or incentive supporting the combination. *Id., Texas Instruments, Inc. v. U.S. International Trade Comm.*, 26 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); The motivation to combine references or elements thereof cannot come from the invention itself. *Heidelberger Druckmaschinen AG,* 30 U.S.P.Q.2d at 1377. When prior art references require selective combinations of teachings, there must be some reason for combination other than the hindsight gleaned from the invention itself. Con*tinental Can Company U.S.A., Inc. v. Monsanto Company, 20* U.S.P.Q. 1746 (Fed. Cir. 1991).

The Court stated that "actual evidence" of a motivation to combine the references is required, "[t]hat is, the showing must be clear and particular. *See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc.,* 157 F.3e at 1352, 48 USPQ2d at 1232 (Fed Cir. 1998). Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Id*

Applicants respectfully submit that the instant rejections do not satisfy this requirement of providing actual evidence of motivation to combine the references. Nowhere in Prusiner is there provided a teaching or suggestion to remove prion protein by a polymeric matrix, less so the specific and selective binding of the prion protein to a polymer matrix. Prusiner's disclosure that prion protein binds to a metal salt comlexing agent does not provide sufficient motivation to use a polymeric material that specifically and selectively binds to the prion protein itself.

One of ordinary skill in the art following the teaching of Prusiner has no reason to look for an agent that binds prion protein directly. There is no suggestion in Prusiner that prion protein may bind to any agent directly without the use of a complexing agent. At best, following Prusiner's teachings, one would be motivated to look into compositions of different complexing agents that may bind to the beads. The Examiner provides no evidence that any polymer matrix was known to directly bind to the prion protein of the invention as claimed with specificity and selectivity. In the absence of such teaching there can be no motivation in the art to combine the references as suggested by the Examiner. It is only in Applicants' disclosure, and not in the art, that one finds the teaching to isolate and remove the prion protein from the sample by the use of a polymer matrix.

Accordingly, Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness over the cited references. Reconsideration and withdrawal of this rejection is respectfully requested.

V. Double Patenting

The Examiner rejects Claims 1-6 and 8-33 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-20 of copending Application No. 10/962, 670.

Applicants respectfully request the Examiner holds the rejection of the claims under obviousness double patenting rejection in abeyance until Applicants receive an indication of allowable subject matter in this application.

CONCLUSION

In light of the above, Applicants respectfully submit that all claims are allowable over the art of record, and a Notice of Allowance is courteously solicited. The foregoing is submitted as a full and complete response to the Office Action mailed June 7, 2006. The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application.

Applicant's undersigned attorney may be reached by telephone at (301) 767-0134. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

Date: Sept 7/06

By: _____

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